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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/294,539	04/19/99	MAW SHENQ	C 23070-948

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EXAMINER	
KUBELIK,A	
ART UNIT	**PAPER NUMBER**
1638	9

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/294,539	Applicant(s) MAW SHENQ ET AL.	
	Examiner Anne Kubelik	Art Unit 1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 July 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-69* is/are pending in the application.

4a) Of the above claim(s) *3,5-12,14-21,23-29,33,35-42,44-51,53-59,61,63-69* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,13,22,30-32,34,43,52,60 and 62* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Applicant's election with traverse of Group II (claims 1-2, 4, 13, 22, 30-32, 34, 43, 52, 60 and 62) in Paper No. 8 is acknowledged. The traversal is on the ground(s) that that all the Groups could be searched without undue burden. This is not found persuasive because a thorough search of each group requires a sequence search of multiple databases for each sequence. This mean separate searches would be required for 9 different sequences. A search on more than one sequence represents a severe burden on PTO resources, because of the rapid growth in database size. Additionally, Applicant is reminded that nucleic acids encoding different proteins are chemically distinct compounds, and thus unrelated.

Thus, claims 1-2, 4, 13, 22, 30-32, 34, 43, 52, 60 and 62 are examined, and claims 3, 5-12, 14-21, 23-29, 33, 35-42, 44-51, 53-59, 61 and 63-69 are withdrawn from consideration as being drawn to nonelected inventions.

The requirement is still deemed proper and is therefore made FINAL.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-2, 4, 30-32, 34 and 60 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for nucleic acids that encode SEQ ID NO:4, does not reasonably provide enablement for all nucleic acids that are 50% identical to SEQ ID NO:3. The specification does not enable any person skilled in the art to which it pertains, or with which

it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are broadly drawn to 50% identical to SEQ ID NO:3, plants transformed with those nucleic acids, and methods of using those nucleic acids to enhance resistance to pathogens in a plant. The instant specification, however, fails to provide guidance for which amino acids of the protein encoded by SEQ ID NO:3 can be altered and to which other amino acids, and which amino acids must not be changed, to maintain the activity of SEQ ID NO:4. The specification also fails to provide guidance for which amino acids can be deleted and which regions of the protein can tolerate insertions and still produce a functional protein.

It cannot be predicted by one of skill in the art that nucleic acids that are 50% identical to SEQ ID NO:3 encode proteins with the same function as that of SEQ ID NO:4. Bowie et al (1990, Science 247:1306-10) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of the protein to fold into unique three-dimensional structures that allows it to function and carry out the instructions of the genome. The cited reference also teaches that the prediction of protein structure from sequence data and, in turn, utilizing predicted structural determinations to ascertain functional aspects of the protein, is extremely complex (pg 1306, left column). Bowie et al teach that while it is known that many amino acid substitutions are possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three-dimensional structure/function relationship, and these regions can tolerate only conservative substitutions or none at all (pg 1306, right column). The sensitivity of proteins to

alterations in even a single amino acid in a sequence is exemplified by Lazar et al (1988, Mol. Cell. Biol. 8:1247-1252), who teach that a replacement of aspartic acid at position 47 with alanine or asparagine in transforming growth factor alpha had no effect, but that replacement with serine or glutamic acid sharply reduced biological activity (see the abstract). Small changes in amino acid sequence can completely modify enzymatic function; Broun et al (1998, Science 282:1315-1317) teach that a change of four amino acids converts an oleate 12-desaturase to a hydroxylase. Thus, Lazar et al and Broun et al demonstrated that one or few amino acid substitutions could dramatically affect the biological activity and the structure-function characteristics of a protein.

Making "conservative" substitutions (*e.g.*, substituting one polar amino acid for another, or one acidic one for another) does not produce predictable results. Lazar et al (*supra*) showed that the "conservative" substitution of glutamic acid for aspartic acid at position 47 reduced biological function of transforming growth factor alpha while "nonconservative" substitutions with alanine or asparagine had no effect (abstract). Similarly, Hill et al (1998, Biochem. Biophys. Res. Comm. 244:573-577) teach when three histidines that are maintained in ADP-glucose pyrophosphorylase across several species are substituted with the "nonconservative" amino acid glutamine, there is little effect on enzyme activity, while the substitution of one of those histidines with the "conservative" amino acid arginine drastically reduced enzyme activity (see Table 1). All these mutated proteins, however, are encoded by nucleic acids that have much more than 50% identity to the original nucleic acid.

Given the claim breath, unpredictability, and lack of guidance as discussed above, undue experimentation would have been required by one skilled in the art to develop and evaluate a

multitude of nucleic acids that are 50% identical to SEQ ID NO:3, plants transformed with those nucleic acids, and methods of using those nucleic acids to enhance resistance to pathogens in a plant.

4. Claims 1-2, 4, 13, 22, 30-32, 34, 43, 52, 60 and 62 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are broadly drawn to methods of producing plants that have enhanced resistance to pathogens by transformation with nucleic acids that have 50% identity to SEQ ID NO:3 or that encode SEQ ID NO:4, as well as to those nucleic acids and plants.

The specification (pgs 28-30) describes the isolation of rice genes that encode protein that can interact with *Arabidopsis* NPR1 in a yeast two-hybrid system. Two of these rice genes (MN1 and PN1) were used in another yeast two-hybrid assay to isolate additional rice genes that encode proteins that interact with proteins encoded by the first set of rice genes. SEQ ID NO:3 (NH1) encodes one of these latter proteins. The specification provides no evidence as to the function of the protein encodes by SEQ ID NO:3, nor does it provide any working examples of plants transformed with SEQ ID NO:3 having enhanced pathogen resistance.

Delaney (2000, Trends Plant Sci. 5:49-51) teach that a number of different kinds of proteins interact with NPR1 and with those proteins that interact with NPR1 (pg 49, column 3, paragraph 3, to pg 50, column 1, paragraph 1; Fig. 2). Some of these proteins are inhibitors of PR (pathogenesis-related) gene expression. If SEQ ID NO:3 encodes a protein that represses or otherwise inhibits PR gene expression, plants transformed with it are likely to have decreased

disease resistance due to overexpression of the inhibitor protein. Additionally, even alteration of proteins known to interact with NPR1 has no effect on induced resistance (pg 49, column 3, paragraph 3). Thus, it cannot be guaranteed that a gene encoding a protein that interacts with a protein that interacts with NPR1 will, when transformed into a plant, produce enhanced disease resistance in that plant.

Given the claim breath, unpredictability, lack of guidance, and lack of working examples as discussed above, undue experimentation would have been required by one skilled in the art to develop and evaluate methods for producing plants that have enhanced resistance to pathogens by transformation with nucleic acids that have 50% identity to SEQ ID NO:3 or that encode SEQ ID NO:4, as well as to those nucleic acids and plants.

5. Claims 1-2, 4, 13, 22, 30-32, 34, 43, 52, 60 and 62 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are broadly drawn to a multitude of DNA molecules that have 50% sequence similarity to SEQ ID NO:3 due to the deletion, insertion or substitution of an unspecified number of nucleotides. In contrast, the specification only describes a coding sequence from rice that comprises SEQ ID NO:3. The claims provide no evidence as to the function of the encoded protein.

Therefore, given the lack of written description in the specification with regard to the structural and physical characteristics of the claimed compositions, and given the high level of

unpredictability in this art, one skilled in the art would not have been in possession of the genus claimed at the time this application was filed.

See *University of California v. Eli Lilly*, 119 F.3d 1559, 43 USPQ 2d 1398 (Fed. Cir. 1997):

> The name cDNA is not in itself a written description of that DNA; it conveys no distinguishing information concerning its identity. While the example provides a process for obtaining human insulin-encoding cDNA, there is no further information in the patent pertaining to that cDNA's relevant structural or physical characteristics; in other words, it thus does not describe human insulin cDNA .... Accordingly, the specification does not provide a written description of the invention ....

See Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ 2d 1016 at page 1021:

> A gene is a chemical compound, albeit a complex one, and ... conception of a chemical compound requires that the inventor be able to define it so as to distinguish it from other materials .... Conception does not occur unless one has a mental picture of the structure of the chemical or is able to define it by its method of preparation, its physical or chemical properties, or whatever characteristics sufficiently distinguish it. It is not sufficient to define it solely by it principal biological property, *e.g.*, encoding human erythropoietin, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claim 1-2, 4, 13, 22, 30-32, 34, 43, 52, 60 and 62 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicant regards as the invention.

Claims 1, 31 and 60 are not written in proper Markush format. The claims should be in the format "selected from the group **consisting of** A, B, C and D." The phrase "selected from the group comprising" should be replaced with "selected from the group consisting of". This phrase occurs twice in each claim. See MPEP 2173.05(h). Dependent claims are included in the rejection.

The terms "enhancing" and "enhanced" in claim 60 are relative terms that render the claim indefinite. The terms "enhancing" and "enhanced" are not defined by the claim, the

specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is suggested that the resistance in the resulting plant be compared to that of a plant that is not transformed with the nucleic acid.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

9. Claims 1, 4, 30-31, 34 and 60 are rejected under 35 U.S.C. 102(e) as being anticipated by Uknes et al (US Patent 5,986,082, filed December, 1996).

Uknes et al teach *Arabidopsis* nucleic acids (SEQ ID NOs:1, 6, 7, 9, 11, 13 and 15) with 56-60.8% similarity to SEQ ID NO:3 of the instant application (see sequence search results). Uknes et al also teach plants transformed with this nucleic acid and a method of using it to enhance disease resistance in a plant (column 22, line 44, to column 28, line 60; column 29, line 25, to column 30, line 12; claims 1-10).

10. Claims 1, 4, 30-32, 34 and 60 are rejected under 35 U.S.C. 102(e) as being anticipated by Ryals et al (US Patent 6,031,153, filed December, 1996).

Ryals et al teach *Arabidopsis* nucleic acids (SEQ ID NOs:1, 6, 7, 9, 11, 13 and 15) with 56-60.8% similarity to SEQ ID NO:3 of the instant application (see sequence search results). Ryals et al also teach plants, including rice, transformed with this nucleic acid and a method of using it to enhance disease resistance in a plant (column 53, line 1, to column 62, line 11; claim 32).

11. Claims 1, 4, 30-31, 34 and 60 are rejected under 35 U.S.C. 102(b) as being anticipated by Ausubel et al (WO98/06748).

Ausubel et al teach a nucleic acid from *Nicotiana glutinosa* (SEQ ID NO:13) that is 64.3% similar to SEQ ID NO:3 of the instant application (see sequence search results). Ausubel et al also teach plants transformed with that nucleic acid and a method of using it to enhance disease resistance in a plant (pg 57, line 21, to pg 59, line 2).

12. Claims 1 and 4 are rejected under 35 U.S.C. 102(b) as being anticipated by Cao et al (1997, Cell 88:57-63).

Cao et al teach a nucleic acid from *Arabidopsis* that is 56% similar to SEQ ID NO:3 (see sequence search results).

13. Claims 13, 22, 43, 52 and 62 are free of the prior art because neither isolated nucleic acids encoding SEQ ID NO:4, nor plants transformed with those nucleic acids, are taught or are reasonably suggested by the prior art. Claim 2 is free of the prior art, because of the failure of the prior art to teach or suggest an isolated nucleic acid from rice that is 50% identical to SEQ ID NO:3 or that encodes SEQ ID NO:4.

Conclusion

14. No claim is allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne R. Kubelik, whose telephone number is (703) 308-5059. The examiner can normally be reached on Monday through Friday, 8:15 am - 4:45 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paula Hutzell, can be reached on (703) 308-4310. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Anne R. Kubelik, Ph.D.
August 6, 2001

DAVID T. FOX
PRIMARY EXAMINER
GROUP ~~180~~ 1638